Omicron Spike endows SARS-CoV-2 with enhanced infectivity and resistance to the interferon-induced antiviral state in primary nasal epithelia

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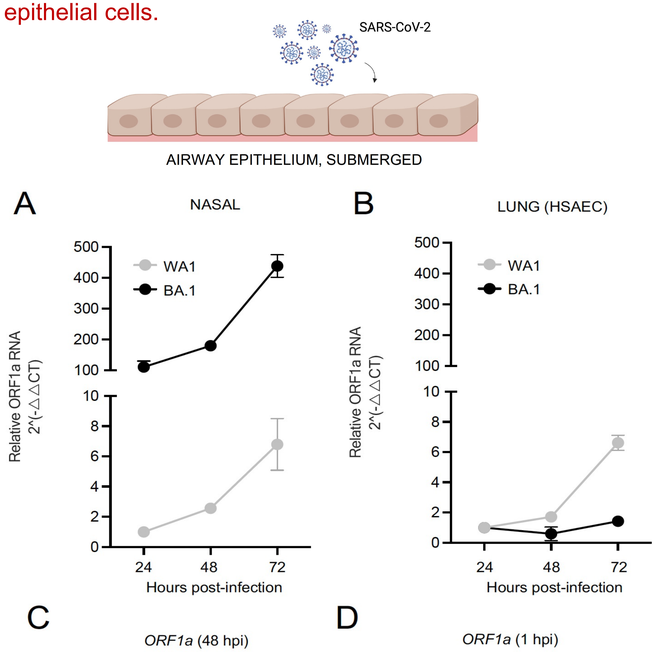
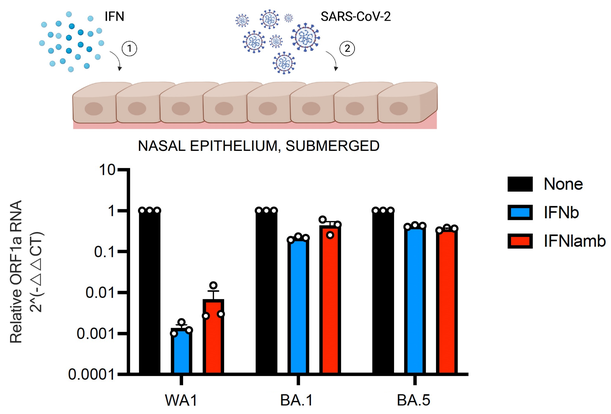
Omicron (BA.1) exhibited enhanced infectivity relative to SARS-CoV-2 isolated early in the pandemic (WA1) in human primary nasal epithelial cells.

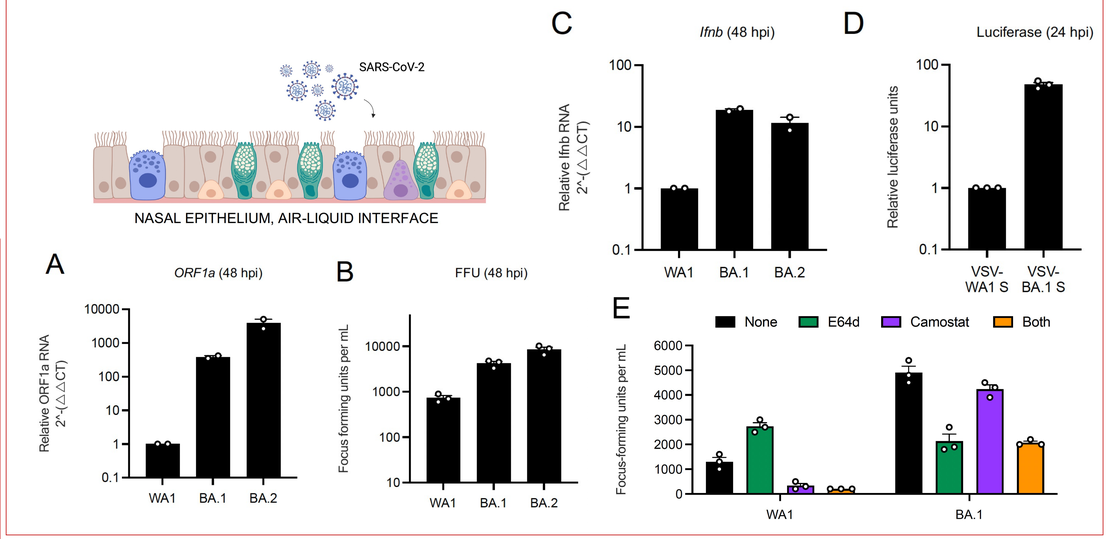


The increased propensity for Omicron to adhere and enter nasal epithelia is associated with a route of cellular entry that enables escape of interferon-induced antiviral defenses.



Omicron lineages, including BA.1 and BA.2, emerged following COVID-19 vaccination campaigns, displaced previous SARS-CoV-2 variants of concern worldwide, and gave rise to sublineages continue to spread among humans. Previous research has shown that Omicron lineages exhibit decreased propensity for lower respiratory tract infection compared to ancestral SARS-CoV-2. Nonetheless, Omicron lineages exhibit an unprecedented transmissibility in humans, which until now has been mostly attributed to escape from vaccine-induced neutralizing antibodies. Here, we show that Omicron lineages exhibit enhanced propensity to infect adult primary nasal epithelia. In primary nasal epithelial cells cultured at the air-liquid interface, which recapitulates the physiological architecture of nasal epithelium in vivo, BA.1 and BA.2 exhibited enhanced infectivity relative to SARS-CoV-2 isolated early in the pandemic (WA1). We found that Omicron Spike enables superior attachment and entry into nasal epithelial cells. Omicron is resistant to both E64d and camostat, suggesting that Omicron variants utilize a distinct and poorly understood route of entry. In contrast to WA1, invasion of nasal epithelia by Omicron BA.1 and BA.2 was accompanied by elevated interferon beta expression. Since Omicron infection in nasal epithelia is associated with robust innate immune response, we tested sensitivity of Omicron BA.1, BA.2, and BA.5 to inhibition by type-I and type-III interferons. All Omicron strains exhibited resistance to type-I and type-III interferons, a finding that was recapitulated by pseudovirus bearing different Spikes. Therefore, the increased propensity for Omicron to adhere and enter nasal epithelia is associated with a route of cellular entry that enables escape of interferon-induced antiviral defenses. Our results suggest that the constellation of Spike mutations unique to Omicron allow for increased adherence to nasal epithelia, flexible usage of virus entry pathways, and interferon resistance. These findings inform our understanding of how Omicron evolved elevated transmissibility between humans despite a decreased propensity to infect lower respiratory tract.

Omicron strains exhibited enhanced infectivity relative to SARS-CoV-2 isolated early in the pandemic (WA1) in primary nasal epithelial cells cultured at the air-liquid interface.



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Omicron strains exhibited resistance to type-I and type-III interferons in primary nasal epithelial cells cultured at the air-liquid interface.

